
Dexamethasone Gel

The invention relates to an ophthalmological preparation containing dexamethasone as the active ingredient and, optionally, also containing the usual additives and water.

Dexamethasone preparations are known in the form of eye-drops and eye ointments. Eye-drops usually have concentrations between 0.05 and 0.1%, whereas eye ointments usually contain about 0.05% dexamethasone sodium phosphate.

Known eye-drop formulations comprising dexamethasone esters as the active ingredient are adjusted to slightly alkaline pH values. For example, solutions of drops which are currently available commercially typically have a pH value of about 7.3. These slightly alkaline values are selected because dexamethasone esters manifest greatest stability in the slightly alkaline range, as is also the case with prednisolone esters.

In this regard, the pH value is typically selected to be as close as possible to neutral, since higher alkalinities are

suspected of causing eye irritations and other tolerance problems.

It is known that the antiphlogistic efficacy of eye-drops is superior to that of eye ointments. In experiments, the bio-availability of eye ointments was substantially poorer than that of eye-drop solutions, even in cases of extended contact times (Cox et al., Arch. Ophthalmol. 88, 549 (1972); Kupferman et al., Arch. Ophthalmol. 91, 373 (1974)).

Although eye-drops manifest a greater bio-availability than ointments, it is often difficult to achieve the desired dwell time, when using solutions of drops. Drop solutions are washed away relatively rapidly, for example by lacrimal fluid, with the result that the concentration of the active ingredient decreases relatively rapidly.

For many applications, it would be advantageous if it were possible to achieve an extended constant concentration of the active ingredient on the eye, after a once-only application. In this regard, recourse may be had to ointments only at the price of considerable drawbacks, owing to the known bio-availability problems.

It is the object of the invention to provide an ophthalmological preparation which does not involve these difficulties.

This object is met by the features as defined in the attached principal claim.

Advantageous further developments and embodiments are defined in the subordinate claims.

The attempt to formulate a gel preparation according to the invention, on the basis of the known drop solutions, such that a suitable gelling agent is added, leads to surprising difficulties.

When working on the basis of the known drop solutions in the pH range of 7 to about 7.3, the addition of carbomer surprisingly leads to a considerable decomposition of the active ingredient after only a short interval, such that the required stability is not achieved.

It appears that there is an intensified conversion of dexamethasone dihydrogen phosphate disodium ("dexamethasone sodium phosphate) into the free base.

Surprisingly, it is possible for this decomposition to be prevented by selecting a higher pH value. Gelling agents, such as Carbopol(R), appear to have an adverse effect on the durability of aqueous dexamethasone phosphate solutions in the acid to neutral range and also in the weakly alkaline range, while, surprisingly, distinctly improving said durability in the more alkaline range.

Accordingly, when carbomers, in particular of the Carbopol 980 NF type or similar Carbopol products, are used as gelling agents in the gels according to the invention, the required stability is provided in the pH range above 7.3.

Storable stable gel preparations at pH values above 7.3, preferably above 7.6 and most preferably at about 7.8 and above, are provided at a concentration of 0.05 to about 1% by mass, preferably between 0.1 and 0.6% by mass and, most preferably, at about 3% by mass of carbomer, in particular of the Carbopol 980 NF type, and active-ingredient concentrations of the order of about 0.1% by mass. The upper limit depends on the ophthalmological compatibility of the preparation, since very high alkalinities may lead to irritations. Accordingly, pH values above 8 will not be used in practice, or only under exceptional circumstances.

The preparation according to the invention is usually adjusted to the required pH value by means of pharmacologically acceptable alkalis, for example sodium hydroxide.

In addition to the active ingredient, the gelling agent and the alkali for adjusting the alkalinity, it also contains a preservative, such as, in particular, benzododecinium chloride (BAC C12), from the group including the benzalkonium chlorides. In addition, the preparation preferably contains an isotonic agent, such as sorbitol, and a chelating agent, such as sodium edetate. Water is used as the solvent for the preparation.

A typical formulation according to the invention for a batch of 100 kg substantially contains the following components:

Designation	Quantity
Dexamethasone dihydrogen phosphate disodium	0.0985 kg
Benzododecinium chloride (BAC C12)	0.0100 kg
Carbopol 980 NF	0.3000 kg
Sorbitol	4.9000 kg
Sodium hydroxide, solid	0.1460-0.1540 kg
Sodium edetate	0.0100 kg
Water for injection purposes	94.5275-94.5355 kg
	100.000 kg

Surprisingly, a preparation of this kind is as stable as a comparable solution of drops, i.e. two or three years. The preparation is very well tolerated when applied, does not cause eye irritations (with the choice of the preservative contributing in this regard), and permits the desired extended dwell time, in the course of which the bio-availability of the active ingredient is not adversely affected, in contrast to drop solutions.